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translator to RWS Group Ltd, of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England declare;

1. That I am a resident of the United Kingdom of Great Britain and Northern Ireland.

2. That I am well acquainted with the German and English languages.

3. That the attached is, to the best of my knowledge and belief, a true translation into the English language of the accompanying copy of the specification filed with the application for a patent in Germany on 19 February 1999 under the number 199 07 080.6 and the official certificate attached hereto.

4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent application in the United States of America or any patent issuing thereon.

For and on behalf of RWS Group Ltd

The 21st day of February 2006

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Method for preparing a carrier (biochip) coated with biologically or chemically functional materials

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Method for preparing a carrier (biochip) coated with biologically or chemically functional materials

Description

The invention relates to the use of an illumination matrix which can be controlled to generate an optionally adjustable exposure pattern in the field of biotechnology in general and for preparing and manipulating biochips in particular.

Miniaturizing and at the same time functionally integrating elements, components and whole systems make novel applications available in many technologies. Said applications extend from sensor technology via microsystem technology (e.g. complex biochips using semiconductor technology) to actuator technology (e.g. in the form of micropumps). The industries extend from classical mechanical engineering via automotive and aviation industries to medical technology and the forward-looking biotechnology. In medical technology, for example, new implants are developed and the pharmaceutical industry advances new technologies for efficient development of novel medicaments and diagnostic systems at enormous cost. Owing to its great potential, biotechnology in particular profits from said development.

Novel methods which make use of the changed peripheral conditions are developed for economical production in the field of microtechnology. The same is true for the inspection techniques required for monitoring the miniaturized processes.

For basic research in the life sciences and for medical diagnostics and some other disciplines, gathering biologically relevant information (mostly in the form of genetic information) in defined examination material

is extraordinarily important. In this context, the genetic information is present in the form of an enormous variety of different nucleic acid sequences, the DNA (deoxyribonucleic acid). Realization of said information leads, via producing transcripts of DNA into RNA (ribonucleic acid), mostly to the synthesis of proteins which for their part are commonly involved in biochemical reactions.

A powerful system format for gathering said wealth of information is the so-called biochip. Detecting particular nucleic acids and determining the sequence of the four bases in the nucleotide chain (sequencing) produces valuable data for research and applied medicine. In medicine, it was possible, to a greatly increasing extent through in-vitro diagnostics (IVD), to develop and provide to the doctor in charge equipment for determining important patient parameters. For many diseases, diagnosis at a sufficiently early stage would be impossible without said equipment. Here, genetic analysis has been established as an important new method (e.g. case diagnosis of infectious diseases such as HIV or HBV, genetic predisposition for particular cancers or other diseases, or in forensic science). Close interaction between basic research and clinical research made it possible to elucidate the molecular causes and (pathological) connections of some diseases down to the level of genetic information. This development, however, has only just started, and greatly intensified efforts are necessary, particularly for the conversion into therapy strategies. Overall, the genome sciences and nucleic acid analysis connected therewith have made important contributions both to the understanding of the molecular bases of life and to the elucidation of very complex diseases and pathological processes. Moreover, genetic analysis or analysis through genetic engineering already now provides a broad spectrum of diagnostic methods.

Further development in medical care is hampered by the explosion in costs related to correspondingly expensive methods. Thus, determining genetic risk factors by sequencing at the moment still costs several hundred to several thousand US dollars. It is necessary here not only to demand implementation of possible diagnostic and therapeutic benefits, but also to advance integration into a workable and affordable health-care system.

Likewise, applying appropriate technologies in research can take place on a large scale and also at universities only if the costs related thereto are reduced. Here, a change in paradigms of research in life sciences begins to emerge:

The bottleneck of deciphering primary genetic information (sequence of bases in the genome) and detecting the state of genetic activity (genes transcribed into messenger RNA) of cells and tissues is removed by the availability of sufficiently cheap and flexible biochips. It is then possible to concentrate work on the (very complex) task of analyzing and combining the relevant data. This should result in new levels of knowledge for biology and subsequently in novel biomedical therapies and diagnostic possibilities.

The biochips already mentioned before are miniaturized hybrid functional elements with biological and technical components, for example biomolecules which are immobilized on a surface (outer surface or/and inner surface) and which may serve as specific interaction partners, and a matrix, for example silicon matrix. Frequently, the structure of said functional elements has rows and columns; this is known as a chip array. Since thousands of biological or biochemical

functional elements may be arranged on a chip, microtechnical methods are usually needed to prepare said elements.

Possible biological and biochemical functional elements are in particular: DNA, RNA, PNA, (in nucleic acids and chemical derivatives thereof, for example, single strands, triplex structures or combinations thereof may be present), saccharides, peptides, proteins (e.g. antibodies, antigens, receptors), derivatives of combinatorial chemistry (e.g. organic molecules), cell components (e.g. organelles), cells, multicellular organisms, and cell aggregates.

In general, biochips have a 2D base area for the coating with biologically or biochemically functional materials. The base areas may also be formed, for example, by walls of one or more capillaries or by channels. An extension of the geometry is a 3D structure in which analyzing and, where appropriate, also manipulating or controlling the reactions take place in a 2D arrangement.

Especially in the USA, enormous resources are used to advance the development of miniaturized biochips.

Regarding the prior art, the following publications are referred to, for example:

1. Nature Genetics, Vol. 21, supplement (complete), Jan. 1999 (BioChips)
2. Nature Biotechnology, Vol. 16, pp. 981-983, Oct. 1998 (BioChips)
3. Trends in Biotechnology, Vol. 16, pp. 301-306, Jul. 1988 (BioChips).

Biochips known to date can be classified in outline form by the following criteria:

Detection principle:

- chromatographic methods;
- interaction of analytes with a solid phase, usually an immobilized interaction partner (e.g. hybridization of nucleic acids to DNA oligonucleotides).

Detection methods (optical, electrical)

- marker-based (e.g. absorption, fluorescence or luminescence) or marker-free detection methods (generation of light to detect reactions);
- presentation for detection (serial, parallel);
- optical detection (serial: in a scanner, or parallel: using a CCD camera).

Assignment of the analyte to its carrier (solid phase)

- (ARRAY: with more than one immobilized interaction partner per carrier, or SINGLE: with only one immobilized interaction partner per carrier);

Preparation methods

- (e.g. synthesizing oligonucleotides in a light-activated manner directly on the biochip, spotting ready-synthesized oligonucleotides, coating beads or tubes);

Types of carriers

- (glass chips, plastic chips, microtiter plates, tubes or beads).

Important application fields for biochips are:

molecular diagnostics (including in-vitro diagnostics, clinical diagnostics, genetic diagnostics)/development of pharmaceuticals (substance development, testing, screening etc.)/biological basic research (i.a. genomics, transcriptomics, proteomics, physiomics)/

molecular interactions/analysis and screening of pathogens (viroids, prions, viruses, prokaryotes, eukaryotes)/oncology/environmental monitoring/food analysis/forensic science/screening of medical products (i.a. blood products)/detection, analysis and screening of transgenics (plants, animals, bacteria, viruses, breeding, outdoor trials)/cytology (i.a. cell assays)/histology/all types of nucleic acid analyses (i.a. sequence analysis, mapping, expression profiles).

With regard to the prior art concerning technologies for preparing biochips, reference is made to photolithographic systems.

A multiplicity of photolithographic systems for exposure-dependent generation of fine and very fine structures using light of different wavelength (energy) of down to below 200 nm are commercially available for applications in semiconductor technology. The finer the structures to be generated, the shorter the wavelength used has to be. Thus, structures in the sub-µm range which are already in the range of visible-light wavelengths (400-800 nm) can only be generated using high energy radiation of distinctly shorter wavelength.

Photolithographic systems consist in principle of a lamp as energy or light source and a photolithographic mask which has transparent and nontransparent areas and thus generates an exposure pattern in the transmitted-light course of ray. Optical elements reproduce said exposure pattern on the object to be exposed (e.g. reduced by a factor of 100). A line on the mask is thereby reduced in width from 0.1 mm to 10 µm. Preparing a microstructure in or on a silicon wafer commonly requires 10 to 30 exposure steps. The systems are geared to said number and facilitate automatic mask switching by means of magazines and operating tools.

Thus, an almost macroscopic structure of the mask results in a microstructured image on the object to be exposed, for example the silicon wafer. To generate a photolithographic mask, photolithographic systems are likewise employed again which, of course, need only a correspondingly lower resolution and also, depending on the preparation method, only a correspondingly smaller energy input. This is a cyclic process which has been very far advanced and perfected due to the large market volume of the semiconductor industry.

GeSim already uses for the production of photolithographic masks LCD photo plotters from Mivatec. This is possible, since the mask structures, with respect to structure size and required wavelength, allow exposure in the visible-light range. This makes a relatively fast and relatively flexible production of masks possible. This is sufficient in semiconductor technology owing to the limited number of masks required, since only a functional test shows the success of the microstructuring and thus there is usually always enough time for producing new or improved masks.

Using photolithography for the light-induced in-situ synthesis of DNA (synthesis directly on the biochip), Affymax Institute and Affymetrix already use commercial exposure systems for preparing high-density DNA microarrays (references: US 5,744,305, US 5,527,681, US 5,143,854, US 5,593,839, US 5,405,783). The wavelength employed is restricted to 300-400 nm. Each change in the exposure pattern requires a mask change. This is extremely restricting since preparing, for example, a DNA array with oligonucleotides of 25 building blocks in length (25-mers) per slot requires approx. 100 individual exposure cycles.

The object of the invention is to provide a method

which facilitates flexible and fast preparation of biochips.

The method of the invention for preparing a carrier (biochip) coated with biologically or biochemically functional materials comprises the following steps:

(a) providing a carrier having a surface which has photoactivatable groups,

(b) activating the photoactivatable groups on at least one predetermined area of the carrier surface by location-specific exposure of the carrier using an illumination matrix which can be controlled to generate an optionally adjustable exposure pattern,

(c) location-specific binding of biologically or chemically functional materials or building blocks for such materials on at least one of the predetermined areas and

(d) where appropriate, repeating the activation and binding steps on the same or/and different predetermined areas.

The use of an illumination matrix which can be controlled to generate an optionally adjustable exposure pattern, facilitates great flexibility in the preparation or/and manipulation of biochips and, in particular, faster preparation of biochips than previously possible. In contrast to generating correspondingly fine-resolution exposure patterns in a photolithography machine by means of invariant individual masks which have to be changed when changing the exposure pattern, using a controllable illumination matrix can in principle generate and alter any possible exposure pattern by simply controlling the illumination matrix from a control computer.

Programmability and electronic controllability of the

illumination matrix remove the exchange and also generation of the mask units as were required for the photolithographic methods. Generating the exposure patterns thus is no longer connected with expenses for preparing, exchanging, positioning, storing and optimizing exposure masks. This makes in particular the in-situ synthesis of biochips (e.g. DNA microarrays) accessible to wide use. According to a preferred embodiment of the invention, an illumination matrix is used which is able to illuminate with a resolution of at least 500 points per cm^2.

The illumination matrix and the assigned light source serve in principle to provide the desired exposure pattern for controlling/exciting photochemical processes or, where appropriate, for analyzing a biochip matrix. According to a variation, it is possible to optionally modulate the light intensity and/or wavelength of each luminous spot of the illumination matrix or of the exposure pattern on the biochip.

The illumination matrix used is preferably a controllable reflection matrix which reflects light location-selectively, according to its control, in a particular direction (here in the direction of the carrier or biochip). Such reflecting surface light modulators having controlled deformable mirror arrangements for generating light patterns can be in particular light modulators having viscoelastic control layers or light modulators having micromechanical mirror arrays. Regarding the technology of such light modulators having viscoelastic control layers and light modulators having micromechanical mirror arrays, relevant data sheets of the Fraunhofer Institute for Microelectronic Circuits and Systems are referred to and are attached to this application. The advantage of such controllable reflection matrices is in particular

that they are available for a wide spectral range from UV to IR light, for example in a wavelength range from 200-2000 nm. A further advantage is that a reflection matrix of this type facilitates an exposure parallel in time of all sites to be exposed in the exposure pattern at appropriate illumination using a light field extending across the matrix area. This possibility of parallel exposure of a biochip has consequences for the length of the preparation (for in-situ syntheses), for the possibilities of online control and evaluation (no artefacts due to time gaps between points of measurement etc.) and for possible manipulations, for example in the case of cell arrays or other biological components of a biochip (for example in the case of retina preparations or light-dependent neuronal activity).

As long as parallel exposure is not crucial, it is possible, instead of uniform illumination of the illumination matrix to carry out screening or scanning of the illumination matrix using a bundled beam, for example a laser beam, in order to generate the desired light pattern on or in the biochip, according to the control of the illumination matrix. It is thus possible to utilize a wide variety of light sources, for example also light sources whose emission spectrum or emission wavelength can be optionally altered, e.g. an N_2 laser, so that, for example, a plurality of signal-generating fluorescent substances on the biochip can be excited using different wavelengths (this is a kind of 2D spectroscopy).

Another class of possible illumination matrices for the use according to the present invention is represented by light source arrays, i.e. matrix-like arrangements of very small light sources which can be controlled individually. These can be, for example, microlaser arrays, microdiode arrays or the like.

Another class of illumination matrices which can be used according to the invention is represented by matrix arrangements of "light valves" or controllable transmitted-light modulators which can be controlled location-selectively in order to let or not to let light through. An important representative of this class of illumination matrices is the controllable liquid crystal matrix or LCD matrix. Regarding the technology of suitable "light valve" arrangements, reference is made inter alia to US 5,728,251, in particular to the suspended particle devices (SPD) technology.

The method of the invention may provide for the carrier to be exposed to pulsating, coherent, monochromatic, parallel radiation or/and, where appropriate, to radiation which can be focused in different planes.

The carrier or biochip may have, for example, a semiconductor surface, a glass surface or a plastic surface for coating with biologically or biochemically functional materials, which surface may be an outer surface or/and an inner surface of the carrier, the latter, as long as the carrier is at least partially hollowed out, for example has channels running through. Preference is given to using a transparent carrier which facilitates optical studies in transmitted light mode.

The predetermined activatable areas may include, for example, an area of from 1 μm^2 to 1 cm^2, in particular 100 μm^2 to 1 mm^2. The predetermined activatable areas may be surrounded by nonactivated or/and nonactivatable areas.

The illumination matrix may have a pattern inherent to the predetermined activatable areas, for example with sites which cause always shading or darkness in the

exposure pattern.

The biologically or biochemically functional materials are selected preferably from biological substances or from materials reacting with biological substances, namely preferably from nucleic acids and nucleic acid building blocks, in particular nucleotides and oligonucleotides, nucleic acid analogs such as PNA and building blocks thereof, peptides and proteins and building blocks thereof, in particular amino acids, saccharides, cells, subcellular preparations such as cell organelles or membrane preparations, viral particles, cell aggregates, allergens, pathogens, pharmacological active substances and diagnostic reagents.

The biologically or biochemically functional materials are preferably synthesized on the carrier in two or more stages from monomeric or/and oligomeric building blocks.

The great flexibility of the method according to the invention facilitates generating an expansive substance library having a multiplicity of different biologically or chemically functional materials on the carrier.
The activation of predetermined areas comprises in particular cleaving a protective group off the carrier itself or off materials or building blocks thereof which are bound on said carrier.

The illumination matrix facilitates a flexible control of the time course of the exposure so that the exposure may take place at a rate in the range of from, for example, 1/10000 to 1000, in particular 1/10 to 100 light patterns per second.

According to a preferred variation of the method, exposure of the carrier is monitored by a light sensor

matrix, in particular a CCD matrix, and, where appropriate, controlled taking into account the information obtained by said monitoring. Preferably, the sensor matrix is arranged opposite to and facing the illumination matrix, with the carrier being positioned between illumination matrix and sensor matrix in order to make transmitted-light observation possible. Alternatively, the illumination matrix, carrier and sensor matrix may also be grouped in a reflected-light arrangement.

The sensor matrix may be used for carrying out automatic recognition and/or, where appropriate, calibration of the particular carrier used by means of an analysis unit connected after the sensor matrix.

A further development of the invention may provide for removing the materials synthesized on the carrier, in particular polymers such as nucleic acids, nucleic acid analogs and proteins in order to provide them for particular purposes. In this aspect, it is possible to make use of the method practically as a preparation method for biochemical materials. In this context, it may be provided for to remove the materials in different areas in successive steps and to use them as building blocks for further synthesis of polymers, in particular nucleic acid polymers.

Further aspects of the invention are given in claims 25 to 40, in particular the use of an illumination matrix which can be controlled to generate an optionally adjustable exposure pattern as light source of a light-emission detector for detecting the optical behavior of a 2- or 3-dimensional test area provided with biologically or biochemically functional materials, the test area being preferably prepared in the light-emission detector.

A further aspect of the invention should be pointed out, according to which a controllable illumination matrix is used for exposing in a spatially resolved manner biochips with cells/tissue sections, in order to carry out exposure-dependent manipulations (light-sensitive processes such as photosynthesis, manipulation of retina preparations, light-dependent neuronal activity) or analyses (as 2D-FACS; cell-array, tissue-derived cell-array).

Some aspects of the invention are illustrated in the following, with respect to the figures. Figures 1-5 depict diagrams of different exemplary embodiments for devices for preparing/manipulating/studying a carrier (biochip) coated with biologically or chemically functional materials. Fig. 6 depicts a cross section of a part of a carrier with integrated illumination matrix.

Fig. 1 depicts a first embodiment of an arrangement for preparing a biochip or/and for manipulating or/and for studying biologically or biochemically functional materials immobilized thereon.

The arrangement according to fig. 1 can be conceptually divided into three groups of functional modules or system modules 2, 4, 6. The system module 2, also called below programmable light source matrix, includes at least one light source 8, at least one illumination matrix 10 which can be controlled to generate an optionally adjustable exposure pattern, and a control computer 12 which may be, for example, a programmable single chip microprocessor which is able to communicate, if required, with an external computer via an appropriate interface and which serves to control the illumination matrix 10 using an appropriate programme. Alternatively, the illumination matrix can be controlled from an external computer, for example

personal computer. The system module 2 may further include optical elements 11, 14 which may be lenses, apertures, masks or the like and which are arranged for possible exchange where appropriate.

The second system module 4 is the exchangeable carrier or biochip which is to be exposed by the programmable light source matrix 2. The third system module 6 is a light detection unit which preferably includes a matrix made of light sensors 16. The matrix 16 is preferably an in particular color-capable CCD sensor chip which can be used for spectrally resolved and intensity-resolved, location-selective measurements. Where appropriate, the system module 6 may also contain optical elements 18 such as lenses, apertures, masks or the like.

The light sensor matrix 16 is arranged opposite and facing the illumination matrix 10, the carrier 4 being located in the (transmitted) light path between the illumination matrix 10 and the light sensor matrix 16.

In the case of the example according to fig. 1, the illumination matrix 10 is an electronically controllable optical component whose transparency can be controlled with spatial resolution according to the resolution of the matrix, i.e. the arrangement and size of the matrix elements which form the matrix and which can be specifically controlled; the transparency can be switched preferably between two states, namely the essentially opaque state and a state of maximum transparency for the light of the light source 8. The illumination matrix 10 therefore can be considered as an electronically adjustable mask in a transmitted light arrangement. Depending on the control by the control computer 12, the illumination matrix 10 generates an exposure pattern which is used for exposing the carrier 4 location-selectively. The

illumination matrix 10 used in the arrangement according to fig. 1 is preferably a liquid crystal matrix (LCD matrix). It is in principle also possible to use other light valve arrangements which can be controlled with spatial resolution, for example microplates, microsliders, etc., in order to realize an illumination matrix 10 of the kind depicted in figure 1.

The detection module 6 may be connected to the computer 12 or, where appropriate, to an external computer, for example personal computer, to control said module and to process the measurement information it provides.

The system modules 2 and 6 are preferably arranged on a shared holder which is not shown in figure 1, and they can be, where appropriate, adjusted relative to one another. The holder further has a sliding guide or the like by means of which the exchangeable carriers 4 can be introduced in each case into the position according to figure 1 in a simple manner and can be removed again from said position for removal of the appropriate carrier 4.

The arrangement according to figure 1 can be used in the preferred manner to coat an appropriate carrier 4 location-selectively with biologically or biochemically functional materials. For this purpose, a carrier 4 is used which has a surface having photoactivatable groups. Examples of suitable carriers are i.a. given in the German patent application 198 39 256.7. The programmable light source matrix 2 is used to generate an exposure pattern on the carrier surface provided with photoactivatable groups, in order to activate the photoactivatable groups in predetermined areas which are exposed to the light of the light source 8 in accordance with the exposure pattern. Via the feed 20, appropriate reagents may be fed to the surface (in

example 2 to an inner surface of the carrier), which contain the desired biologically or biochemically functional materials or building blocks for such materials which are then able to bind to the predetermined areas. 21 denotes a discharge tubing for the reagents.

The biologically or biochemically functional materials or building blocks may for their part be provided with photoactivatable groups which can be activated by area in a possible subsequent activation step in accordance with the chosen exposure pattern, in order to bind in a further binding step biologically or biochemically functional materials or building blocks for such materials corresponding to the reagents employed. Not listed above were possible washing steps to flush the reagents used last, prior to the respective next exposure step. Depending on the activation wavelength of the photoactivatable groups, the exchangeable light source 8 may be a particular radiation source emitting in the infrared range, in the visible range, in the ultraviolet range or/and in the X-ray range.

Exposure, washing and binding steps can be repeated in a specifically controlled manner in order to generate, for example, a high-density microarray of biomolecules such as, for example, DNA, RNA or PNA.

Applications of this type do not necessarily require the light detection module 6; it is, however, possible to utilize said module expediently for online quality control of the processes which are light-dependent and take place in or on the biochip 4, i.e., for example, for monitoring an in-situ synthesis of biomolecules for preparing a microarray. The light sensor matrix 16 facilitates monitoring with spatial resolution the light-dependent processes via optical signals.

The light detection module 6 may generally be used for graduating or calibrating the system prior to a synthesis or analysis or other reactions or manipulations on the biochip.

The light sensor matrix 16 may, where appropriate, also be used for type recognition in which, for example, a carrier or chip body assigned to particular applications is automatically detected and the reactions and settings during subsequent processes are automatically adjusted.

By using the optical elements 14, it is possible to focus the two-dimensional exposure pattern, where appropriate, in one or more particular planes in or on the biochip. Shifting the focusing plane during a process is also conceivable.

Figure 2 depicts a diagram of a second embodiment of an arrangement for preparing, studying and/or manipulating a biochip. Elements in figs. 2 - 6 which correspond in their function to elements in fig. 1 are marked with in each case corresponding indicators so that in this respect the description of the first exemplary embodiment can be referred to. In the embodiment according to fig. 2, the illumination matrix provided for is an electronically controllable reflection matrix 10a. The electronically controllable reflection matrix 10a used may be, for example, a high-resolution surface light modulator with viscoelastic control layer and mirror layer. Such surface light modulators with viscoelastic control layers are illustrated, for example, in the data sheet, attached as appendix to the present application, entitled "Lichtmodulatoren mit viskoelastischen Steuerschichten" [Light modulators with viscoelastic control layers] which has been published by the Fraunhofer Institute for Microelectronic Circuits and Systems, D 01109 Dresden,

Germany. Reflection surface light modulators have also been developed by Texas Instruments. Such a surface light modulator allows generation of an exposure pattern with spatial resolution for exposing the carrier or biochip 4.

Alternatively, the electronically controllable reflection matrix 10a used may also be a surface light modulator with one or more micromechanical mirror arrays as is illustrated in the data sheet, attached as appendix to the present application, entitled "Lichtmodulatoren mit mikromechanischen Spiegelarrays" [Light modulators with micromechanical mirror arrays] which has been published by the Fraunhofer Institute for Microelectronic Circuits and Systems, D 01109 Dresden, Germany.

Very generally, such electronically controllable mirror matrices are very well suited to the requirements of the present invention, since they can be employed over a broad spectral range, in particular also in the UV range in order to generate the desired exposure patterns.

Direction of the light path according to fig. 2 additionally requires a light deflection element 24 which may be, for example, a partly transparent mirror which deflects the light coming from the light source 8 to the reflection matrix 10a and allows the light which is reflected back from the reflection matrix 10a to pass through downward to the biochip 4 so that it is possible to utilize on the biochip 4 or, where appropriate, in the biochip 4 the exposure pattern generated in accordance with the control of the reflection matrix 10a for photoactivating, analyzing or manipulating biochemical processes.

Fig. 3 shows a variation of the embodiment according to

fig. 2, in which the embodiment of fig. 3 has a light path for which the deflection element denoted as 24 in fig. 2 can be dispensed with, since the controllable reflection matrix 10a is arranged such that it can deflect light coming from the light source 8 to the biochip 4 in accordance with the chosen exposure pattern.

Fig. 4 depicts a diagram of another embodiment of an arrangement for preparing, studying or/and manipulating a biochip of the present invention. In the embodiment according to fig. 4, the illumination matrix used is a matrix arrangement 10b made of light sources, for example a microlaser array or a microdiode array. At the moment developments are taking place which are aimed at putting a multiplicity of microscopically small semiconductor lasers as tiny powerful light sources on a single chip. A controllable "light chip" of this type could be used as matrix 10b. Regarding literature on the background of the "light chips", the journals: Nature 3, 97, pp. 294-295, 1999 and MPG-Spiegel 4/98, pp. 13-17 may be referred to for example.

Fig. 5 shows an arrangement in which the detection module 6 with sensor matrix 16 is set up for reflected light or backlight observation of the biochip 4.

All arrangements according to figures 1-5 can be used as light-emission detectors for detecting the optical behavior of a biochip test area provided with biologically or biochemically functional materials. This may take place in a manner as is disclosed in the German patent application 198 39 254.0.

Fig. 6 shows a section through an embodiment of a carrier 4 of the invention, said embodiment being distinguished by the illumination matrix 10 being part of the carrier body 4. In this case, the illumination

matrix used is preferably an LCD or SPD matrix which can be disposed of together with its chip carrier 4, after the biochip is no longer used.

In the exemplary case of fig. 6, the carrier body 4 has capillary channels 30 whose walls serve as preparation surface for the coating with biologically or biochemically functional materials. The channels 30 can be selectively charged with the appropriate reagents. The following details are detectable in fig. 6: boundary layers 32 with transparent and nontransparent areas 34 and 35, respectively, transparent electrodes 36 with SPD particles (suspended particles) enclosed between and to be influenced by the electrodes 36, or alternatively liquid crystals 38.

Claims

1. A method for preparing a carrier (biochip) coated with biologically or chemically functional materials, which comprises the steps of:
   (a) providing a carrier having a surface which has photoactivatable groups,
   (b) activating the photoactivatable groups on at least one predetermined area of the carrier surface by location-specific exposure of the carrier using an illumination matrix which can be controlled to generate an optionally adjustable exposure pattern,
   (c) location-specific binding of biologically or chemically functional materials or building blocks for such materials on at least one of the predetermined areas and
   (d) where appropriate, repeating the activation and binding steps on the same or/and different predetermined areas.

2. The method as claimed in claim 1,
characterized in that
electromagnetic radiation in the IR range, visible range, UV range or/and X-ray range is used for the exposure.

3. The method as claimed in claim 1 or 2,
characterized in that
the carrier is exposed to pulsating, coherent, monochromatic, parallel radiation or/and, where appropriate, to radiation which can be focused in different planes.

4. The method as claimed in any of the preceding claims,
characterized in that,
different predetermined areas are exposed

parallel.

5. The method as claimed in any of claims 1 to 4, **characterized in that,** the illumination matrix used is a reflection matrix, in particular a reflection matrix having a mirror arrangement deformable in a controlled way.

6. The method as claimed in any of claims 1 to 4, **characterized in that,** the reflection matrix used is a light modulator with viscoelastic control layers or a light modulator with micromechanical mirror arrays.

7. The method as claimed in any of claims 1 to 4, **characterized in that,** the illumination matrix used is a matrix arrangement which is preferably prepared on a chip and which is composed of light sources or individually controllable areas of one light source, in particular a laser array or/and a diode array.

8. The method as claimed in any of the preceding claims, **characterized in that,** an optically transparent carrier is used.

9. The method as claimed in any of the preceding claims, **characterized in that,** the carrier has a surface selected from semiconducting materials, for example silicon, germanium or gallium arsenide, glass, for example quartz glass, and plastics.

10. The method as claimed in any of the preceding claims,

characterized in that
the predetermined activated areas include an area of from 1 μm^2 to 1 cm^2, in particular 100 μm^2 to 1 mm^2.

11. The method as claimed in any of the preceding claims,
characterized in that
the predetermined activatable areas are surrounded by nonactivated or/and nonactivatable areas.

12. The method as claimed in claim 11,
characterized in that
the illumination matrix has a pattern inherent for the predetermined activatable areas.

13. The method as claimed in any of the preceding claims,
characterized in that
the biologically or chemically functional materials are selected from biological substances or materials reacting with biological substances.

14. The method as claimed in any of the preceding claims,
characterized in that
the biologically or chemically functional materials are selected from nucleic acids and nucleic acid building blocks, in particular nucleotides and oligonucleotides, nucleic acid analogs such as PNA and building blocks thereof, peptides and proteins and building blocks thereof, in particular amino acids, saccharides, cells, subcellular preparations such as cell organelles or membrane preparations, viral particles, cell aggregates, allergens, pathogens, pharmacological active substances and diagnostic reagents.

15. The method as claimed in any of the preceding claims,
characterized in that
the biologically or chemically functional materials are synthesized on the carrier in two or more stages from monomeric or/and oligomeric building blocks.

16. The method as claimed in any of the preceding claims,
characterized in that
a substance library comprising a multiplicity of different biologically or chemically functional materials is generated on the carrier.

17. The method as claimed in any of the preceding claims,
characterized in that
activation of predetermined areas comprises cleaving a protective group off the carrier itself or off materials or building blocks thereof which are bound on said carrier.

18. The method as claimed in any of the preceding claims,
characterized in that
the exposure takes place at a rate of from 1/10000 to 1000, preferably 1/10 to 100 light patterns per second.

19. The method as claimed in any of the preceding claims,
characterized in that
exposure of the carrier is monitored and, where appropriate, controlled by a sensor matrix, in particular a CCD matrix.

20. The method as claimed in claim 19,

characterized in that
the illumination matrix, carrier and sensor matrix form a transmitted-light arrangement.

21. The method as claimed in claim 19,
characterized in that
the illumination matrix, carrier and sensor matrix form a reflected-light arrangement.

22. The method as claimed in any of claims 19 to 21,
characterized in that
the carrier is precalibrated using the illumination matrix and sensor matrix.

23. The method as claimed in any of the preceding claims, which furthermore comprises removing, at least partially, materials synthesized on the carrier, in particular polymers such as nucleic acids, nucleic acid analogs and proteins.

24. The method as claimed in claim 23,
characterized in that
the materials in different areas are removed in successive steps and used as building blocks for further synthesis of polymers, in particular nucleic acid polymers.

25. The use of an illumination matrix, which can be controlled to generate an optionally adjustable exposure pattern, for preparing a carrier coated with biologically or chemically functional materials.

26. The use as claimed in claim 25,
characterized in that
the carrier comprises a multiplicity of different materials, in particular biological materials.

27. The use of a controllable illumination matrix, in particular reflection matrix, in a light-emission detector for detecting the optical behavior of a 2- or 3-dimensional test area provided with biologically or chemically functional materials.

28. The use as claimed in claim 27,
characterized in that
the test area is prepared in the light-emission detector.

29. The use as claimed in claim 27 or 28,
characterized in that
the test area is selected from coated carriers, smears, for example of cells or microbeads, and biological samples, for example tissue sections or cell arrays.

30. The use as claimed in any of claims 27 to 29 in connection with a light detection matrix, in particular a CCD matrix.

31. A method for synthesizing polymers,
characterized in that
a multiplicity of oligomeric building blocks are synthesized on a carrier in parallel steps, are removed from the carrier and brought into contact with each other to synthesize the polymer.

32. The method as claimed in claim 31,
characterized in that
double-stranded nucleic acid polymers of at least 300 bp, in particular at least 1000 bp, in length are synthesized.

33. The method as claimed in either of claims 31 and 32,
characterized in that

nucleic acid polymers selected from genes, gene clusters, chromosomes, viral and bacterial genomes or sections thereof are synthesized.

34. The method as claimed in any of claims 31 to 33, **characterized in that**
the oligomeric building blocks are from 5 to 150, preferably 5 to 30, monomeric units in length.

35. The method as claimed in any of claims 31 to 34, **characterized in that**
in successive steps in each case partial complementary oligonucleotide building blocks are removed from the carrier and brought into contact with each other or with the polymer intermediate product under hybridization conditions.

36. A device for carrying out the method as claimed in any of the preceding claims, which comprises an illumination matrix (10) which can be controlled to generate an optionally adjustable exposure pattern, a frame carrying the illumination matrix (10) and, where appropriate, a light source (8) assigned to the illumination matrix (10), a programmable controller (12) for controlling the illumination matrix (10), a carrier holder located on the frame for accommodating and specifically positioning a relevant carrier (biochip) (4) relative to the illumination matrix (10) such that light patterns generated by the illumination matrix (10) can be projected onto the relevant surface of the carrier (4).

37. The device as claimed in claim 36, wherein the illumination matrix is a reflection matrix, a light source matrix or an illumination matrix

which can be location-selectively controlled with respect to its optical transparency.

38. The device as claimed in either of claims 36 and 37, wherein an optical detector (6) for observing the carrier (4) is provided.

39. The device as claimed in claim 38, wherein the optical detector (6) includes a sensor matrix (16), in particular CCD sensor.

40. A biochip or carrier to be prepared as a biochip as claimed in any of the preceding claims, wherein the carrier (4) has an illumination matrix which can be controlled to generate an optionally adjustable exposure pattern, in particular a liquid crystal matrix (fig. 6).

Abstract

The invention relates to the use of an illumination matrix which can be controlled to generate an optionally adjustable exposure pattern in the field of biotechnology and, more specifically, for preparing and manipulating biochips in particular, with such an illumination matrix being employed for generating exposure patterns on or in said biochip. Preference is given to the illumination matrix used being a reflection matrix having a mirror arrangement deformable in a controlled way.

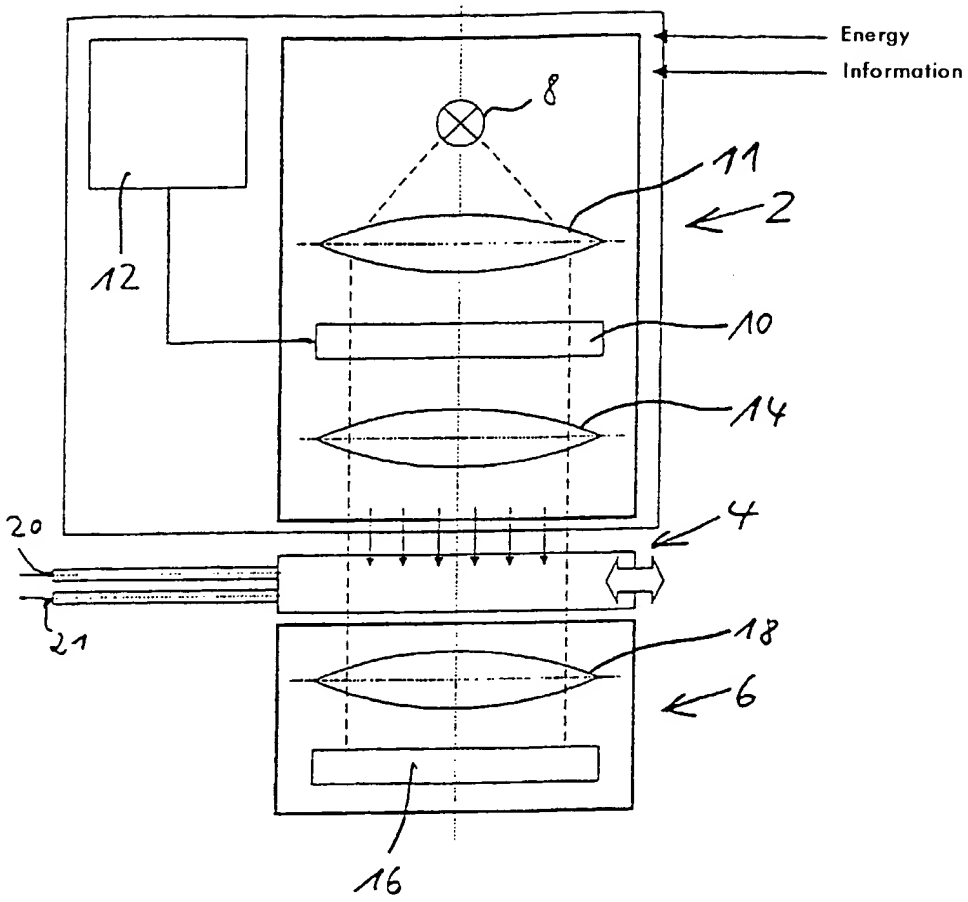

Fig. 1

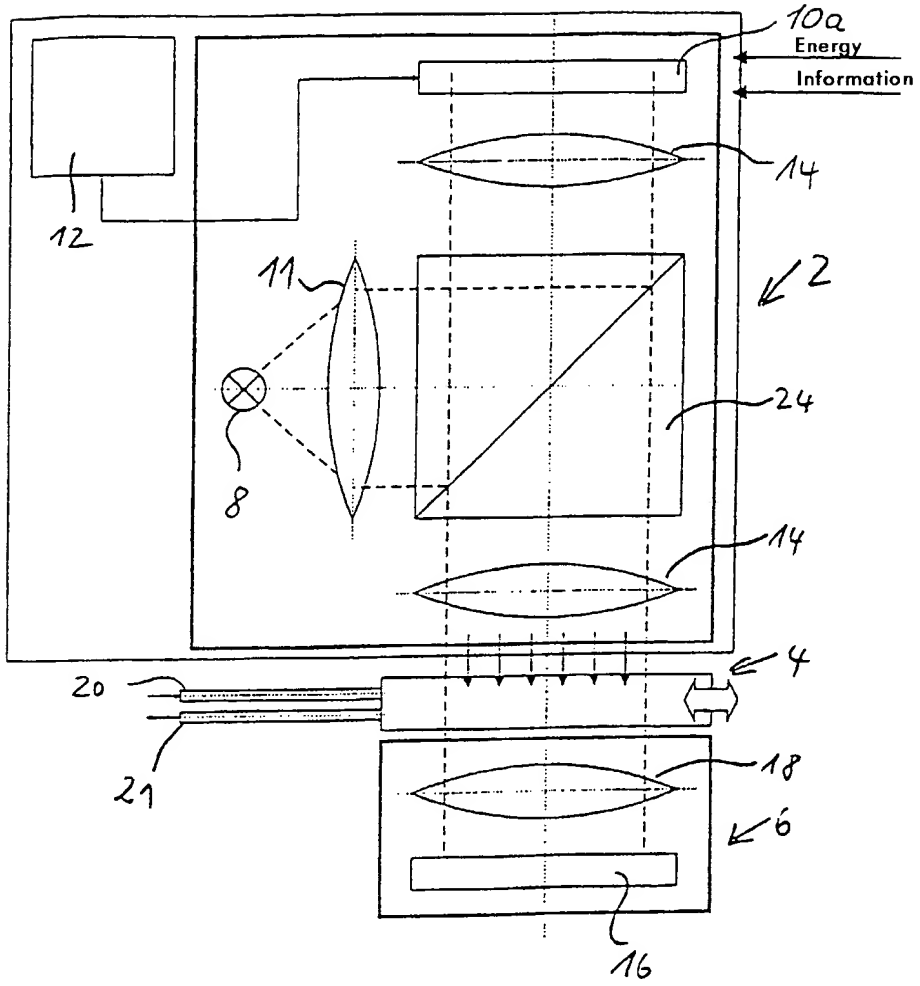

Fig.2

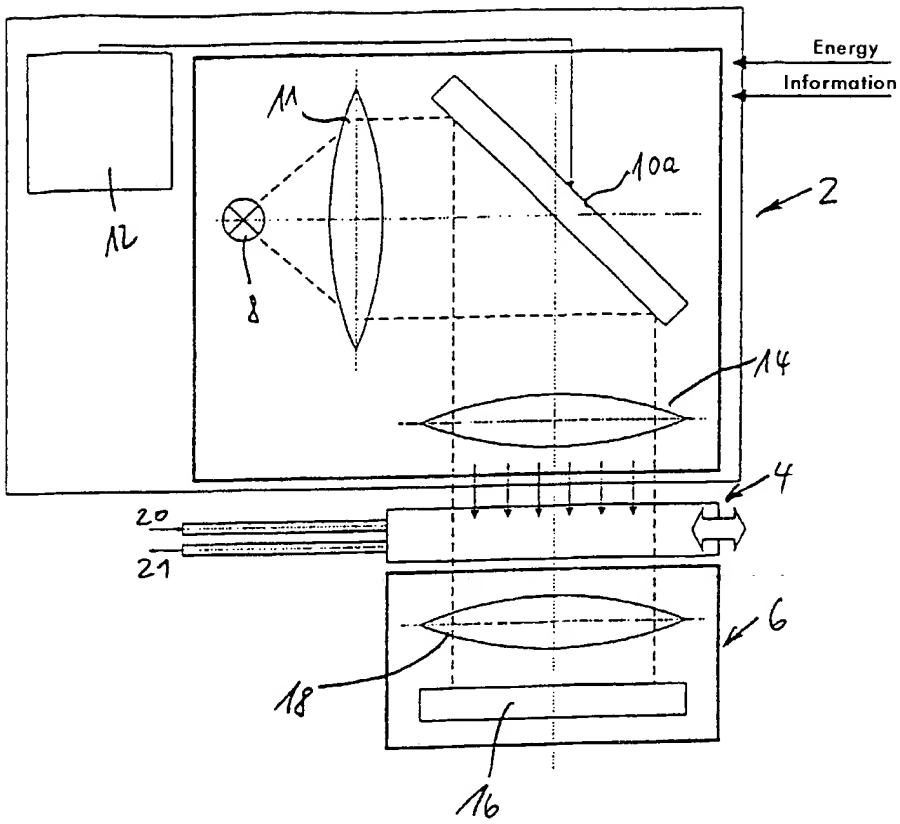

Fig. 3

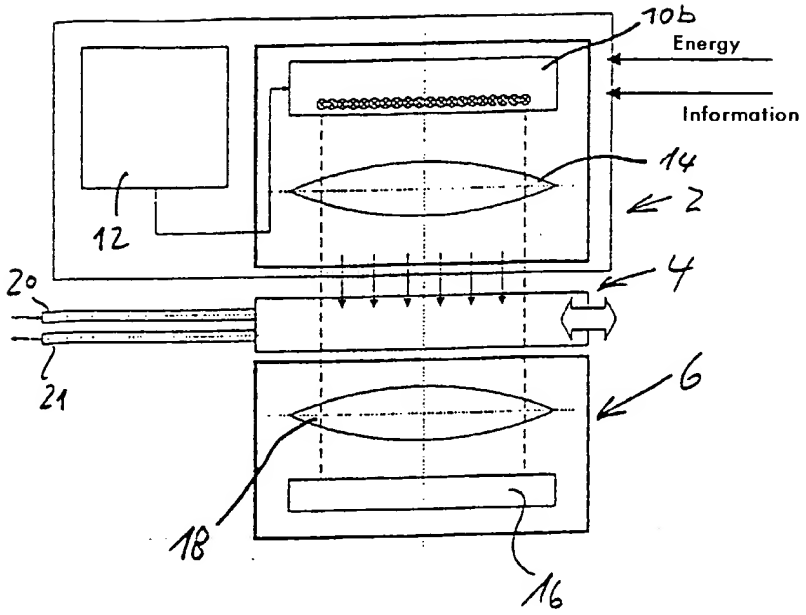

Fig. 4

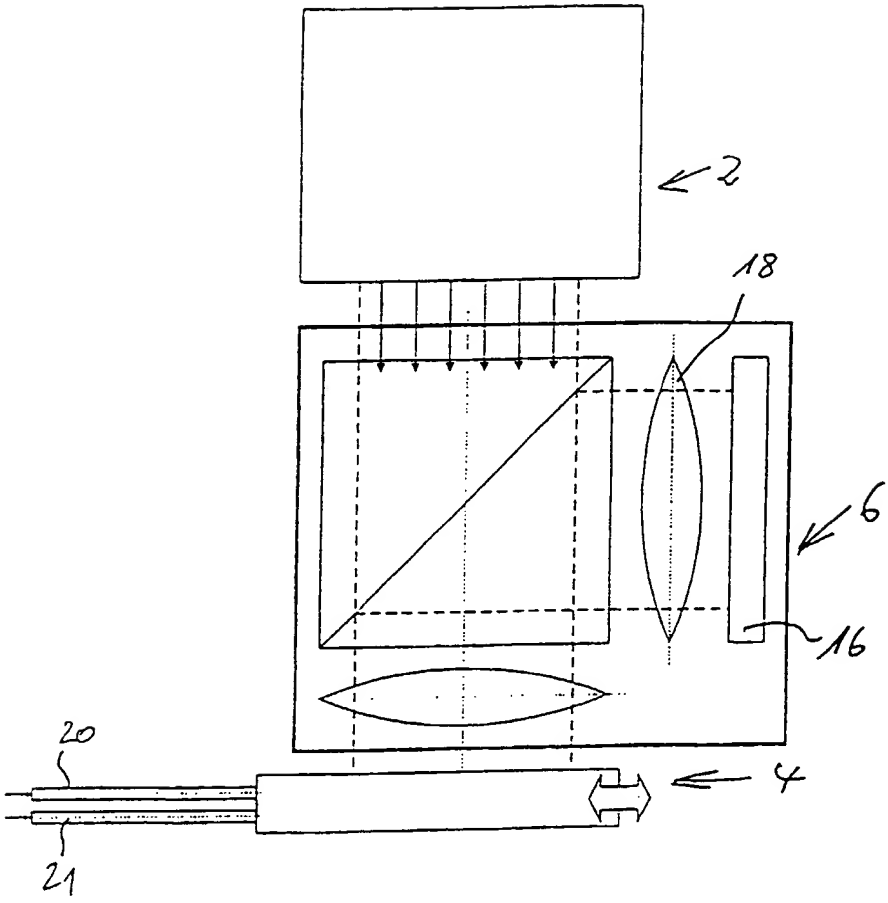

Fig. 5

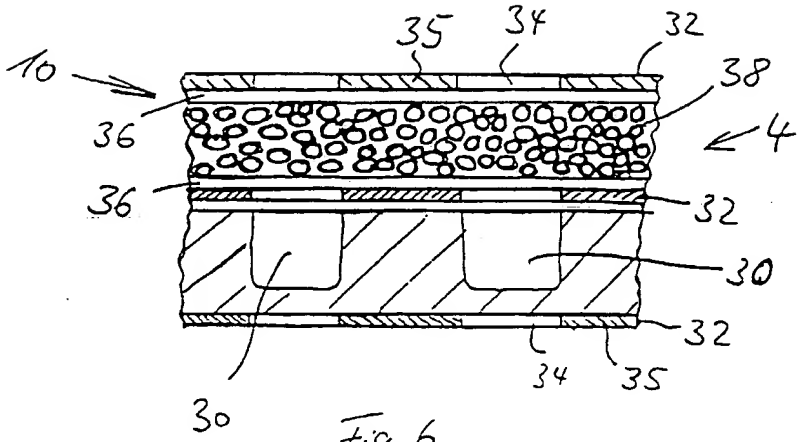

Fig. 6